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Nucleosides. CXLVIII. Synthesis of 6-(β-D-Ribofuranosyl)picolinamide. A Novel *C*-Nucleoside from D-Ribonolactone

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Treatment of 2,4:3,5-di-*O*-benzylidene-D-*aldehydo*-ribose (**1**) with 2-bromo-6-lithiopyridine afforded a mixture of the *altro* and *allo* isomers of 6-(2,4:3,5-di-*O*-benzylidene-D-pentitol-1-yl)-2-bromopyridine (**2** and **3**, respectively). These isomers were chromatographically separated. Compound **2** was converted into 6-(β-D-ribofuranosyl)-2-bromopyridine (**6**) by mesylation of the 1′-hydroxyl group of **2** followed by treatment with trifluoroacetic acid. In a similar manner, the α-isomer **7** was prepared from **3**. The same pyridine-*C*-nucleosides, **6** and **7**, were also synthesized from the commercially available D-ribonolactone in seven steps.

The bromo function of **2** and **3** was converted into the carboxamide group to give 6-(2,4:3,5-di-*O*-benzylidene-D-*altro*-pentitol-1-yl)picolinamide (**10**) and its *allo* isomer **11**. Mesylation of **10** followed by trifluoroacetic acid treatment afforded 6-(β-D-ribofuranosyl)picolinamide (**14**). Similar treatment of **11** gave the α counterpart **15**.

Keywords——new *C*-nucleoside; D-ribonolactone; tiazofurin analogue; 6-(2-bromopyridin-6-yl)-2,3-*O*-benzylidene-5-*O*-tetrahydropyranyl-D-ribofuranose; 6-(β-D-ribofuranosyl)-2-bromopyridine; 6-(α-D-ribofuranosyl)-2-bromopyridine; 6-(β-D-ribofuranosyl)picolinamide; 6-(α-D-ribofuranosyl)picolinamide

Recently, we synthesized[1] 5-(β-D-ribofuranosyl)nicotinamide and its *N*-methylated derivative, which are the *C*-nucleosides isosteric and isoelectronic, respectively, to natural nicotinamide riboside, by condensation of 3-bromo-5-lithiopyridine with 2,4:3,5-di-*O*-benzylidene-D-*aldehydo*-ribose (**1**) followed by conversion of the bromo function into carboxamido group. There has been a persisting belief that sulfur is isosteric to vinylene since the time of Erlenmeyer[2] who first made use of this concept to explain the similarity between benzene and thiophene. Actually, an benzoazepin which can be considered a chlorpromazine analogue in which the sulfur of the phenothiazine of the latter is replaced by vinylene also exhibit tranquilizer activity.[3] Thus, we intended to synthesize 6-(β-D-ribofuranosyl)picolinamide (**14**) which can be viewed as an isostere of the potent anticancer agent, tiazofurin.[4]

Reaction of **1** (Chart 1) with 2-bromo-6-lithiopyridine in a mixture of hexane and tetrahydrofuran (THF) at −78 °C gave a mixture from which the *altro* and *allo* isomers (**2** and **3**) were isolated in 19 and 23% yield, respectively, which were acetylated to **2a** and **3a** for characterization by ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectroscopy. After mesylation of **2** and **3**, the corresponding 1′-mesylates **4** and **5** were treated with trifluoroacetic acid (TFA) in chloroform. From the *altro* isomer **4**, the β-*C*-nucleoside **6** was obtained, and the *allo* intermediate **5** afforded the α-*C*-nucleoside **7**. This in turn supported the assignment of the *altro* and *allo* intermediate structures **2** and **3**.

Compounds **2** and **3** were converted into the corresponding picolinamides, **10** and **11**, by lithiation, carboxylation, and esterification with CH_2N_2 to give the corresponding methyl

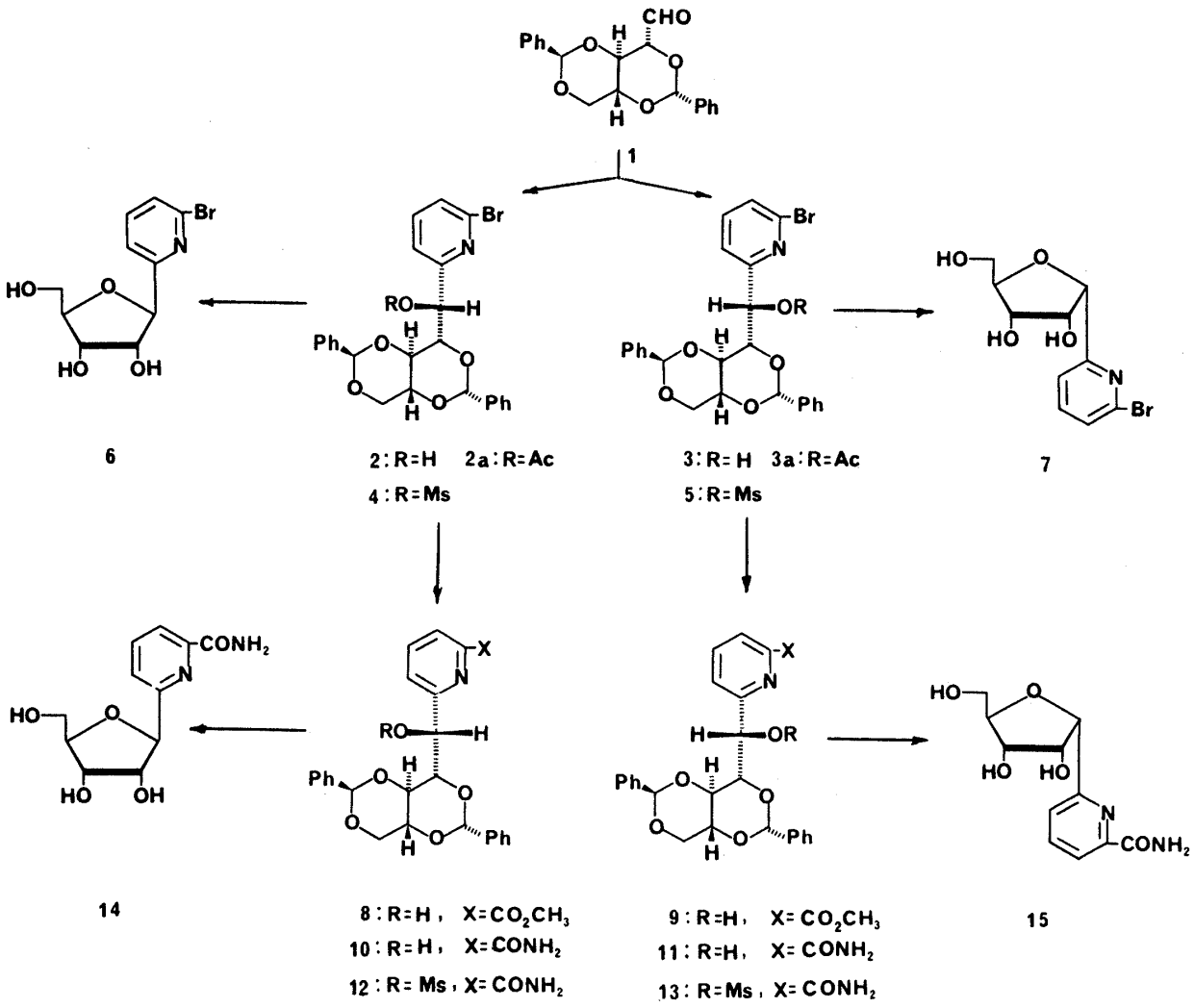

Chart 1

picolinates, **8** and **9**, which were treated with NH_3–MeOH. Conversion of **10** and **11** into their corresponding mesylates, **12** and **13**, followed by solvolysis with trifluoroacetic acid afforded the desired 6-(β-D-ribofuranosyl)picolinamide (**14**) from **12**, and its α-isomer **15** from **13**. A similar synthesis of 2-ribosylpyridine was also reported.[5]

Prerequisite of the syntheses of these *C*-nucleosides was to prepare **1** from D-ribose *via* the diethylmercaptide and the method was not only inefficient but also inappropriate for large-scale synthesis. Ogura and Takahashi[6] has synthesized 1-(pyridin-2-yl)-2,3 : 5,6-di-*O*-isopropylidene-α-L-gulofuranose by condensation of 2,3 : 5,6-di-*O*-isopropylidene-L-gulono-lactone and 2-lithiopyridine. We, therefore, applied their method to commercially available D-ribonolactone for the synthesis of our desired *C*-nucleosides.

D-Ribonolactone (**16**) was converted in two steps to the known[7] 2,3-*O*-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-D-ribonolactone (**17**) (Chart 2) in high yield as a mixture of diastereomers. Treatment of **17** with 2-bromo-6-lithiopyridine afforded the diastereomeric 1-(2-bromopyridin-6-yl)-2,3-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-D-ribofuranose **18** in *ca.* 65% yield. One of the diastereomers was obtained in crystalline form which we assign 1-(2-bromopyridin-6-yl)-2,3-*O*-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-β-D-ribofuranose (**18**) on the following basis: The difference in chemical shifts of two methyl isopropylidene signals was large (16 Hz) in $CDCl_3$ but very small (4 Hz) in Me_2SO-d_6. It is therefore impossible to use the Imbach's rule[8] for the assignment of anomeric configuration. In the 1′-

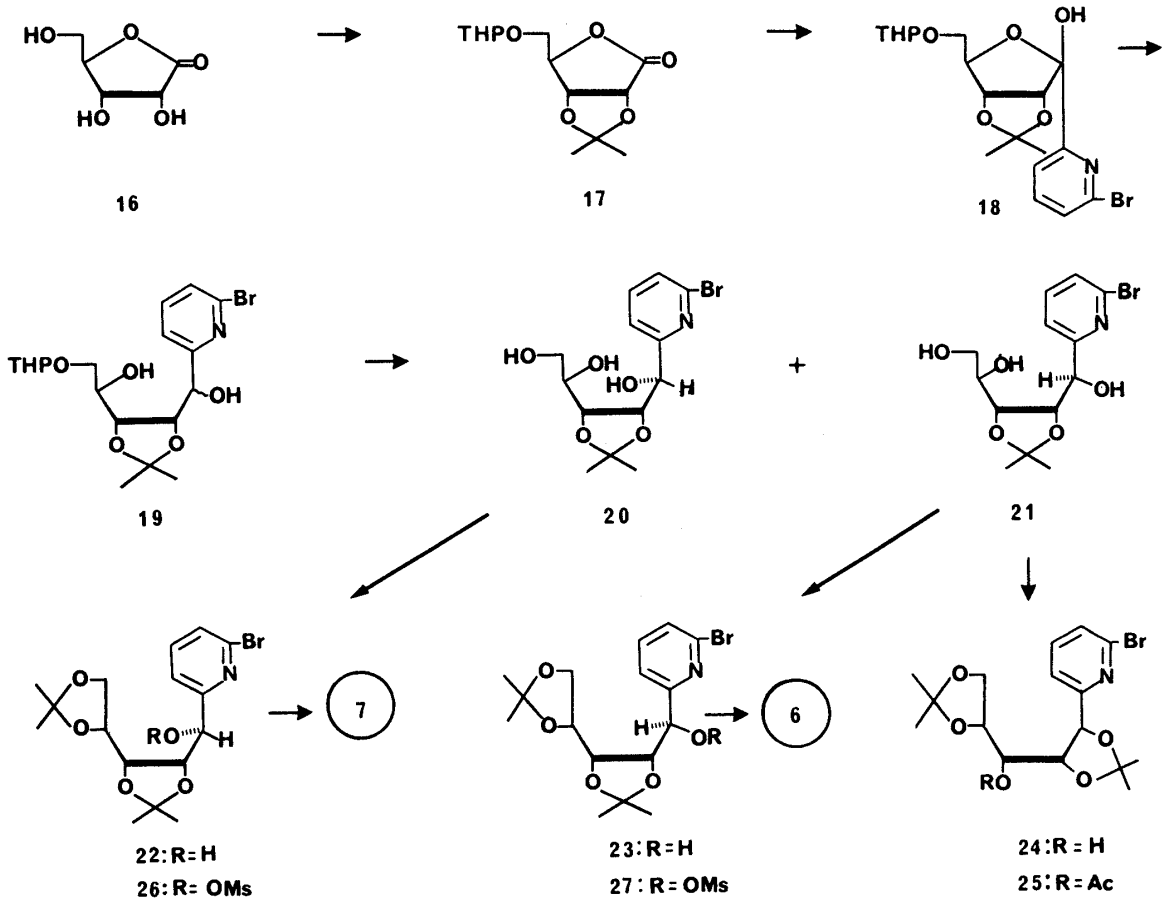

Chart 2

O-acetyl derivative, however, the H-2′ signal showed considerable paramagnetic shift indicating that H-2′ and 1′-OH in **18** are on the same side of the lacton ring, *i.e.*, the β configuration.

Upon treatment of crystalline **18** with $NaBH_4$, a *ca.* 4:1 *allo*/*altro* **19** mixture was obtained. The same mixture **19** was obtained from the diastereomeric **18**. After removal of the tetrahydropyran-2-yl group from **19**, the crystalline *allo*-pentitolylpyridine **20** and its *altro* isomer **21** were separated by chromatography. The *altro* isomer **21** was treated with acetone and *p*-toluenesulfonic acid to give 6-(2,3:4,5-di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (**23**) which slowly isomerized to the 1,2:4,5-di-*O*-isopropylidiene derivative **24** in an acidic medium. Compound **23** was mesylated to **27** which, upon treatment with TFA was converted into the β-*C*-nucleoside **6**.[1,9] In a similar manner, the *allo* isomer **20** was further isopropylidenated to **22** which, after mesylation to **26** followed by solvolysis, afforded the α-*C*-nucleoside **7**.

6-(β-D-Ribofuranosyl)picolinamide (**14**) showed weak inhibitory activity against L1210/0, P815/0, HL-60 and CCRF-CEM cell lines with ID_{50} values of 4.06, 206, 290 and 74.8 μM.

Experimental

General Methods——Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL FX90Q Spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), dd (double doublet), dm (double multiplet). Values given for coupling constants are of first order. Thin layer chromatography (TLC) was performed on Uniplates (Analtech Co., Newark, DE) and

column chromatography on Woelm silica gel (70—230 mesh). Microanalyses were performed by M.H.W. Laboratories, Phoenix, AZ. Mass spectra (MS) (chemical ionization) were taken at the Rockefeller University, Mass Spectrometric Biotechnology Resources Facility.

6-(2,4:3,5-Di-*O*-benzylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (2) and 6-(2,4:3,5-Di-*O*-benzylidene-*allo*-pentitol-1-yl)-2-bromopyridine (3)——To a solution of 2,6-dibromopyridine (2.18 g, 9.2 mmol) in dry Et_2O (100 ml) was slowly added a solution of *n*-BuLi (3.68 ml, 2.5 M solution in hexane, 9.6 mmol) at −78 °C under argon atmosphere. After addition was completed, the reaction mixture was stirred for 15 min. A solution of **1** (1.0 g, 3.06 mmol) in THF (10 ml) was added to the reaction, and then the mixture was allowed to warm slowly to room temperature. Water (50 ml) was added, the organic layer separated. The aqueous layer was washed with Et_2O (3 × 25 ml). The combined organic layer and extracts were washed with brine (3 × 20 ml), dried (Na_2SO_4), concentrated, and the residue chromatographed on a silica gel column using successively 6, 8 and 12% EtOAc–hexane as the eluents. The *allo* isomer **3** was eluted from the column first, followed by the *altro* isomer **2**.

Compound **2** (282 mg, 19%) was obtained as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.90—4.05 (3H, m, H-4′,5′,5″), 4.34—4.44 (2H, m, H-2′,3′), 4.85—5.10 (1H, br d, H-1′), 5.66 (2H, s, =CHPh), 7.24—7.49 (13H, m, =CHPh and H-3,4,5). MS *m/z*: 484 (MH^+, 100). Acetate **2a** was obtained as a foam from **2** (70 mg) with Ac_2O and 4-(dimethylamino)pyridine (DMAP). ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s, Ac), 3.79—3.94 (3H, m, H-4′,5′,5″), 4.45—4.58 (2H, m, H-2′,3′), 5.57 (1H, s, =CHPh), 5.64 (1H, s, =CHPh), 6.20 (1H, d, H-1′, $J_{1',2'}$ = 3.0 Hz), 7.00—7.69 (13H, m, =CHPh, H-3,4,5). *Anal.* Calcd for $C_{26}H_{24}BrNO_6$: C, 59.32; H, 4.59; N, 2.66. Found: C, 59.52; H, 4.70; N, 2.47. The *allo* isomer **3** (340 mg, 23%) was obtained also as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.83—4.02 (3H, m, H-4′,5′,5″), 4.32—4.45 (2H, m, H-2′,3′), 5.14 (1H, dd, H-1′, collapsed to d on addition of D_2O, $J_{1',2'}$ = 3.0 Hz), 5.50 (1H, s, =CHPh), 5.78 (1H, s, =CHPh), 7.05—7.52 (13H, m, Ph, H-3,4,5). MS *m/z*: 484 (MH^+, 100). ^{1}H-NMR of acetate **3a** ($CDCl_3$) δ: 2.08 (3H, s, Ac), 3.84—3.93 (3H, m, H-4′,5′,5″), 4.32—4.65 (2H, m, H-2′,3′), 5.58 (1H, s, =CHPh), 5.75 (1H, s, =CHPh), 6.21 (1H, d, H-1′, $J_{1',2'}$ = 3.6 Hz), 7.25—7.48 (13H, m, Ph, H-3,4,5). *Anal.* Calcd for $C_{26}H_{24}BrNO_6$: C, 59.32; H, 4.59; N, 2.66. Found: C, 59.22; H, 4.73; N, 2.53.

6-(2,4:3,5-Di-*O*-benzylidene-1-*O*-mesyl-D-*altro*-pentitol-1-yl)-2-bromopyridine (4)——A mixture of **2** (50 mg, 0.1 mmol) in CH_2Cl_2 (4 ml) containing Et_3N (0.1 ml, 0.72 mmol) and catalytic amount of DMAP was treated with MsCl (30 μl, 0.38 mmol) at room temperature. The mixture was stirred for 30 min, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using hexane–EtOAc (19 : 1) as the eluent to give **4** (50 mg, 86%) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (3H, s, Ms), 3.92—4.08 (3H, m, H-4′,5′,5″), 4.38—4.52 (2H, m, H-2′,3′), 5.62 (1H, s, =CHPh), 5.65 (1H, s, =CHPh), 5.93 (1H, d, H-1′, $J_{1',2'}$ = 3.0 Hz), 7.25—7.57 (13H, m, Ph, H-3,4,5). MS *m/z*: 562 (MH^+, 100), 107 ($PhCHOH^+$, 30).

In a similar manner, 6-(2,4 : 3,5 di-*O*-benzylidene-D-*allo*-pentitol-1-yl)-2-bromopyridine (**5**) was obtained as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, s, Ms), 3.86—3.93 (3H, m, H-4′,5′,5″), 4.25—4.39 (1H, m, H-3′), 4.72—4.86 (1H, m, H-2′), 5.51 (1H, s, =CHPh), 5.84 (1H, s, =CHPh), 5.90 (1H, d, H-1′, $J_{1',2'}$ = 2.5 Hz), 7.59—7.95 (13H, m, Ph, H-3,4,5). MS *m/z*: 562 (MH^+, 100), 107 ($PhCHOH^+$, 40).

6-(β-D-Ribofuranosyl)-2-bromopyridine (6)——A solution of **4** (40 mg, 0.07 mmol) in a mixture of CF_3CO_2H and $CHCl_3$ (4 : 1, v/v) (3 ml) was stirred for 20 min at room temperature. Water (10 ml) was added, and the aqueous layer was washed with Et_2O (3 × 10 ml). The aqueous layer was then concentrated *in vacuo*, and the residue chromatographed on a silica gel column using $CHCl_3$–MeOH (9 : 1, v/v) as the eluent to give **5** (15 mg, 73%) as a foam. ^{1}H-NMR (Me_2SO-d_6) δ: 3.46—4.01 (5H, m, H-2′,3′,4′,5′,5″), 4.66 (1H, d, H-1′, $J_{1',2'}$ = 4.1 Hz), 7.47—7.85 (3H, H-3,4,5). *Anal.* Calcd for $C_{10}H_{12}BrNO_4 \cdot 1.5H_2O$: C, 37.87; H, 3.86; N, 4.42. Found: C, 37.97; H, 4.20; N, 4.32. Contamination of 1.5 mol of H_2O was detected in the ^{1}H-NMR spectrum of this analytical sample.

In a similar manner, 6-(α-D-ribofuranosyl)-2-bromopyridine (**7**) was obtained in 70% yield also as a foam. ^{1}H-NMR (Me_2SO-d_6) δ: 3.48—4.16 (5H, m, H-2′,3′,4′,5′,5″), 4.94 (1H, d, H-1′, $J_{1',2'}$ = 3.0 Hz), 7.39—7.81 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{10}H_{12}BrNO_4$: C, 41.40; H, 4.17; N, 4.83. Found: C, 41.27; H, 4.20; N, 4.77.

Methyl 6-(2,4:3,5-Di-*O*-benzylidene-D-*altro*-pentitol-1-yl)picolinate (8)——To a solution of **2** (200 mg, 0.43 mmol) in a mixture of hexamethylphosphoramide (HMPA) (0.25 ml) and Et_2O (5 ml) was added a solution of *n*-BuLi (2 ml of 2.5 M solution in hexane, 5 mmol) under argon atmosphere at −78 °C. After the addition, the mixture was stirred at −78 °C for 15 min. A large excess of solid CO_2 was added, and the mixture was allowed to warm to room temperature. The mixture was acidified with 1 N HCl to pH 4. The organic layer was washed with brine (3 × 5 ml), dried (Na_2SO_4), and filtered. The filtrate was cooled to 0 °C, and treated with large excess of CH_2N_2. Excess CH_2N_2 was destroyed by addition of HOAc. The mixture was concentrated *in vacuo*, and the residue chromatographed on a silica gel column using hexane–EtOAc (3 : 1) to give **8** (122 mg, 64%) as colorless crystals, mp 176—179 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s, Me), 3.95—4.43 (5H, m, H-2′,3′,4′,5′,5″), 5.25 (1H, br s, H-1′), 5.64 (1H, s, =CHPh), 5.67 (1H, s, =CHPh), 7.31—8.07 (13H, m, Ph, H-3,4,5). MS *m/z*: 464 (MH^+, 100), 107 ($PhCHOH^+$, 80).

Similar treatment of **3** (200 mg) with *n*-BuLi and CO_2 resulted in the formation of methyl 6-(2,4 : 3,5-di-*O*-benzylidene-D-*allo*-pentitol-1-yl)picolinate (**9**) (115 mg, 60%) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.97 (3H, s, Me), 3.45—4.51 (5H, m, H-2′,3′,4′,5′,5″), 5.28 (1H, d, H-1′, $J_{1',2'}$ = 2.5 Hz), 5.49 (1H, s, =CHPh), 5.79 (1H, s, =CHPh), 6.95—8.02 (13H, m, Ph, H-3,4,5). MS *m/z*: 464 (MH^+, 100), 107 ($PhCHOH^+$, 75).

6-(2,4:3,5-Di-*O*-benzylidene-D-*altro*-pentitol-1-yl)picolinamide (10)——A mixture of **8** (700 mg, 1.56 mmol) and a catalytic amount of NaH in saturated NH_3–MeOH (50 ml) was stirred at room temperature overnight. The solvent was removed, and the residue chromatographed on a silica gel column ($CHCl_3$–MeOH, 49:1) to give **10** (620 mg, 92%) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.92—4.09 (3H, m, H-4′,5′,5″), 4.40—4.47 (2H, m, H-2′,3′), 5.12 (1H, br s, H-1′), 5.66 (1H, s, PhCH), 5.71 (1H, s, PhCH), 7.31—8.17 (13H, m, Ph, H-3,4,5). MS *m/z*: 449 (MH^+, 50), 107 ($PhCHOH^+$, 100).

In a similar manner, 6-(2,4:3,5-di-*O*-benzylidene-D-*allo*-pentitol-1-yl)picolinamide (**11**) was obtained from **9** in 89% as colorless crystals, mp 201—203 °C (from hexane–EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 3.83—4.10 (3H, m, H-4′,5′,5″), 4.29—4.56 (2H, m, H-2′,3′), 5.19 (1H, dd, H-1′, became d on addition of D_2O, $J_{1',2'}=3.3$ Hz), 5.51 (1H, s, PhCH), 5.78 (1H, s, PhCH), 7.11—8.07 (13H, Ph, H-3,4,5). *Anal.* Calcd for $C_{25}H_{24}N_2O_4$: C, 66.95; H, 5.39; N, 6.24. Found: C, 66.60; H, 5.45; N, 6.18.

6-(2,4:3,5-Di-*O*-benzylidene-1-*O*-mesyl-D-*altro*-pentitol-1-yl)picolinamide (12)——A mixture of **10** (50 mg, 0.11 mmol) in CH_2Cl_2 (4 ml) containing Et_3N (100 μl, 0.72 mmol) and a catalytic amount of DMAP and MsCl (30 μl, 0.38 mmol) was stirred at room temperature for 30 min, and then concentrated *in vacuo*. After chromatography on a silica gel column (CH_2Cl_2–MeOH, 49:1, v/v), **12** (49 mg, 83%) was obtained as colorless crystals (from hexane–Et_2O), mp 109—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (3H, s, Ms), 3.94—4.09 (3H, m, H-4′,5′,5″), 4.35—4.48 (2H, m, H-2′,3′), 5.61 (1H, s, PhCH), 5.68 (1H, s, PhCH), 6.03 (1H, d, H-1′, $J_{1',2'}=2.5$ Hz), 7.25—7.43 (10H, m, Ph), 7.65—8.19 (3H, m, H-3,4,5). MS *m/z*: 527 (MH^+, 100).

In a similar manner, 6-(2,4:3,5-di-*O*-benzylidene-1-*O*-mesyl-D-*allo*-pentitol-1-yl)picolinamide (**13**) was obtained in 87% yield as a foam from **11**. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, s, Ms), 3.84—3.91 (3H, m, H-4′,5′,5″), 4.24 (1H, m, H-3′), 4.42 (1H, m, H-2′), 5.50 (1H, s, PhCH), 5.83 (1H, s, PhCH), 5.99 (1H, d, H-1′, $J_{1',2'}=2.5$ Hz), 7.04—8.20 (13H, m, Ph, H-3,4,5). MS *m/z*: 527 (MH^+, 100).

6-(β-D-Ribofuranosyl)picolinamide (14)——Compound **12** (32 mg, 0.06 mmol) was dissolved in a 4:1 mixture of CF_3CO_2H and $CHCl_3$ (v/v) (3 ml), and the solution stirred for 20 min at room temperature. The reaction was quenched by addition of H_2O, and the aqueous layer was separated, washed with Et_2O (3 × 10 ml), and then concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$–MeOH, 9:1, v/v) to give **14** (10 mg, 64%) as a colorless syrup. ^{1}H-NMR (Me_2SO-d_6) δ: 3.91—3.96 (2H, m, H-5′,5″), 4.01—4.19 (3H, m, H-2′,3′,4′), 4.73—4.89 (3H, m, H-1′, 2 × OH, collapsed to d at δ4.77 by addition of D_2O, $J_{1',2'}=4.9$ Hz), 7.68—8.00 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 51.61; H, 5.82; N, 10.77.

By similar treatment of **13** (28 mg, 0.06 mmol), 6-(α-D-ribofuranosyl)picolinamide (**15**) (8 mg, 57%) was obtained as a syrup. ^{1}H-NMR (Me_2SO-d_6) δ: 3.56—4.22 (5H, m, H-2′,3′,4′,5′,5″), 5.04 (1H, d, H-1′, $J_{1',2'}=0.5$ Hz), 7.33—7.94 (3H, m, H-3,4,5). MS *m/z*: 255 (MH^+, 100).

1-(2-Bromopyridin-6-yl)-2,3-*O*-isopropylidene-5-*O*-(tetrahydropyran-2-yl)-β-D-ribofuranose (18)——To a solution of 2,6-dibromopyridine (6.1 g, 25.7 mmol) in dry Et_2O (250 ml) was slowly added a solution of *n*-BuLi (10.3 ml of 2.5 M solution in hexane, 25.7 mmol) below −50 °C under argon atmosphere. After addition was completed, the mixture was stirred for 15 min. To this mixture was added dropwise a solution of **17** (5.0 g, 18.4 mmol) in THF (40 ml). The mixture was allowed to warm slowly (2 h) to room temperature. The reaction was quenched by addition of H_2O (50 ml). The aqueous layer was extracted with Et_2O (3 × 30 ml). The combined organic layer and extracts were washed (H_2O, 30 ml), dried (Na_2SO_4), concentrated *in vacuo*, and the residue chromatographed (hexane–EtOAc, 9:1) to give an 1:1 diastereomeric mixture of **18** (6.12 g, 63.5%) as a syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, iso-Pr), 1.43 (3H, s, iso-Pr), 1.43—1.67 (6H, m, THP), 3.59—4.10 (4H, m, H-5′,5″, THP), 4.47—5.00 (4H, m, H-2′,3′,4′, THP), 5.45 (1/2H, s, OH), 5.52 (1/2H, s, OH), 7.26—7.65 (3H, m, H-3,4,5), ^{1}H-NMR (Me_2SO-d_6) δ: 1.18 (3H, s, iso-Pr), 1.22 (3H, s, iso-Pr).

One of the diastereomers was crystallized from $CHCl_3$–hexane, mp 144—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, iso-Pr), 1.44 (3H, s, iso-Pr), 1.51—1.71 (6H, m, THP), 3.59—4.10 (4H, m, H-5′,5″, THP), 4.52 (1H, dt, H-4′, $J_{3',4'}=1.4$, $J_{4',5'}=J_{4',5''}=5.7$ Hz), 4.65—4.76 (2H, m, H-2′,3′), 4.92 (1H, dd, THP), 5.50 (1H, s, OH), 7.26—7.71 (3H, m, H-3,4,5), (Me_2SO-d_6) δ: 1.18 (3H, s, iso-Pr), 1.22 (3H, s, iso-Pr). MS *m/z*: 430 (MH^+, 30), 348 (MH^+ − THP, 60). *Anal.* Calcd for $C_{18}H_{24}BrNO_6$: C, 50.24; H, 5.62; N, 3.26. Found: C, 50.23; H, 5.65; N, 3.21.

A small amount of 1:1 diastereomeric mixture of **18** was acetylated with Ac_2O and DMAP in CH_2Cl_2. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, s, iso-Pr), 1.28 (3H, s, iso-Pr), 1.54—1.75 (6H, m, THP), 2.05 (3H, s, Ac), 3.42—3.89 (4H, m, H-5′,5″, THP), 4.63 (2H, m, H-3′,4′), 4.92—5.03 (1H, m, H-2′), 7.27—7.69 (3H, m, H-3,4,5).

6-[2,3-*O*-Isopropylidene-5-*O*-(tetrahydropyran-2-yl)-D-pentitol-1-yl]-2-bromopyridine (19)——Crystalline **18** (3.2 g, 7.44 mmol) was dissolved in MeOH (50 ml) and treated with $NaBH_4$ (1.0 g, 27 mmol). The mixture was stirred at room temperature for 1 h, then concentrated *in vacuo*. The residue was partitioned between Et_2O (150 ml) and H_2O (150 ml). The organic layer was separated, dried (Na_2SO_4), concentrated *in vacuo*, and the residue chromatographed on a silica gel column ($CHCl_3$–EtOH, 19:1, v/v) to give an *allo*/*altro* mixture **19** (3.05 g, 95%) as an oil which solidified when stored at room temperature, mp 109—111 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27, 1.30, 1.44, 1.48 (total 6H, four s, iso-Pr), 1.49—1.79 (6H, m, THP), 3.61—5.03 (11H, m, H-1′,2′,3′,4′,5′,5″, THP, two OH), 7.26—7.65 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{18}H_{26}BrNO_6$: C, 50.01; H, 6.06; N, 3.24. Found: C, 50.09; H, 6.12; N, 3.17.

Reduction of the diastereomeric mixture of **18** gave the identical *allo*/*altro* product **19**.

6-(2,3-*O*-Isopropylidene-D-*allo*-pentitol-1-yl)-2-bromopyridine (20) and 6-(2,3-*O*-Isopropylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (21)——The above mixture **19** (920 mg, 2.13 mmol) was dissolved in MeOH (5 ml) containing a catalytic amount of TsOH (*ca.* 2 mg). The mixture was stirred at room temperature, and the reaction was monitored by TLC ($CHCl_3$–EtOH, 19 : 1, v/v). When the reaction was completed, the mixture was neutralized with NH_3–MeOH, and then concentrated *in vacuo*. The residue was chromatographed on a silica gel column using successively $CHCl_3$, $CHCl_3$ containing 1, 2 and 5% of EtOH as the eluents. The *allo* isomer **20** was eluted first from the column and was crystallized from EtOAc–hexane (478 mg, 64%), mp 124—125 °C. ^{1}H-NMR (Me_2SO-d_6) δ: 1.16 (3H, s, iso-Pr), 1.24 (3H, s, iso-Pr), 3.49—4.76 (7H, m, H-1′,2′,3′,4′,5′,5″ and 5′-OH: upon addition of D_2O, H-1′ appeared at δ 4.69 as d, $J_{1',2'}$ = 9.0 Hz), 5.10 (1H, d, OH), 6.20 (1H, d, OH), 7.43—7.83 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{13}H_{18}BrNO_5$: C, 44.84; H, 5.21; N, 4.02. Found: C, 44.81; H, 5.25; N, 3.99.

The *altro* isomer **21** (157 mg, 18%) was then eluted from the column, mp 102—104 °C. ^{1}H-NMR (Me_2SO-d_6) δ: 1.18 (3H, s, iso-Pr), 1.42 (3H, s, iso-Pr), 3.57—3.68 (2H, m, H-5′,5″), 4.05—4.36 (2H, m, H-3′,4′), 4.55 (2H, m, H-2′, OH), 4.96 (2H, m, H-1′, OH: upon addition of D_2O, m became s), 5.30 (1H, d, OH), 7.41—7.83 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{13}H_{18}BrNO_5$: C, 44.84; H, 5.21; N, 4.02. Found: C, 44.68; H, 5.20; N, 4.13.

6-(2,3 : 4,5-Di-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-2-bromopyridine (22)——A mixture of **20** (700 mg, 2 mmol) and TsOH (*ca.* 3 mg) in Me_2CO (10 ml) was stirred at room temperature until **20** disappeared (1.5 h, monitored by TLC, $CHCl_3$–EtOH, 19 : 1, v/v). The mixture was neutralized with NH_3–MeOH, precipitated salts removed by filtration, the filtrate concentrated *in vacuo*, and the residue purified by column chromatography ($CHCl_3$–EtOH, 19 : 1, v/v), and crystallized from $CHCl_3$–hexane to give **22** (663 mg, 85%), mp 104—106 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, s, iso-Pr), 1.39 (6H, s, iso-Pr), 1.43 (3H, s, iso-Pr), 4.00—4.56 (6H, m, H-2′,3′,4′,5′,5″, OH), 4.89 (1H, dd, H-1′, collapsed to d upon D_2O addition, $J_{1',2'}$ = 9.0 Hz), 7.34—7.66 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{16}H_{22}BrNO_5$: C, 49.50; H, 5.71; N, 3.61. Found: C, 49.67; H, 5.82; N, 3.67.

6-(2,3 : 4,5-Di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (23)——In a similar manner as above **21** was converted into **23** which was obtained in 79% as a foam. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, s, iso-Pr), 1.34 (3H, s, iso-Pr), 1.41 (3H, s, iso-Pr), 1.47 (3H, s, iso-Pr), 3.43 (1H, d, OH), 3.86—4.27 (3H, m, H-4′,5′,5″), 4.48—4.78 (2H, m, H-2′,3′), 5.11 (1H, d, H-1′, collapsed to s upon D_2O exchange), 7.26—7.58 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{16}H_{22}BrNO_5$: C, 49.50; H, 5.71; N, 3.61. Found: C, 49.22; H, 5.78; N, 3.53.

6-(1,2 : 4,5-Di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (24)——A mixture of **21** (174 mg, 0.5 mmol) and TsOH (*ca.* 3 mg) in Me_2CO (3 ml) was stirred at room temperature for 72 h, and then concentrated *in vacuo*. The residue was chromatographed on a silica gel column using $CHCl_3$–EtOH (19 : 1, v/v) as the eluent to give **24** (130 mg, 70%) as a syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s, iso-Pr), 1.41 (3H, s, iso-Pr), 1.47 (3H, s, iso-Pr), 1.51 (3H, s, iso-Pr), 3.80 (1H, d, OH), 3.93—4.43 (5H, m, H-2′,3′,4′,5′,5″), 5.06 (1H, d, H-1′, $J_{1',2'}$ = 7.4 Hz), 7.26—7.69 (3H, m, H-3,4,5). Acetylation of this product (100 mg) with Ac_2O in CH_2Cl_2 containing DMAP (3 mg) gave 6-(3-*O*-acetyl-1,2 : 4,5-di-*O*-isopropylidene-D-*altro*-pentitol-1-yl)-2-bromopyridine (**25**) (100 mg, 90%) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, iso-Pr), 1.34 (3H, s, iso-Pr), 1.50 (6H, s, iso-Pr), 2.09 (3H, s, Ac), 3.79—4.55 (4H, m, H-2′,4′,5′,5″), 5.08 (1H, d, H-1′, $J_{1',2'}$ = 7.9 Hz), 5.45 (1H, t, H-3′, $J_{2',3'} = J_{3',4'}$ = 5.2 Hz), 7.32—7.67 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{18}H_{24}BrNO_6$: C, 50.24; H, 5.62; N, 3.25. Found: C, 50.20; H, 5.72; N, 3.20.

6-(2,3 : 4,5-Di-*O*-isopropylidene-1-*O*-mesyl-D-*allo*-pentitol-1-yl)-2-bromopyridine (26)——To a mixture of **22** (520 mg, 1.34 mmol), DMAP (5 mg) and Et_3N (360 μl, 2.6 mmol) in CH_2Cl_2 (5 ml) was added MsCl (180 μl, 2.3 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated, and the residue chromatographed on a silica gel column ($CHCl_3$) to give **26** (560 mg, 90%) as a syrup which became a low melting solid upon standing at room temperature. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (12H, s, iso-Pr), 2.96 (3H, s, Ms), 3.82—4.51 (4H, m, H-3′,4′,5′,5″), 4.84 (1H, dd, H-2′, $J_{1',2'}$ = 6.6, $J_{2',3'}$ = 5.5 Hz), 5.79 (1H, d, H-1′, $J_{1',2'}$ = 6.6 Hz), 7.38—7.69 (3H, m, H-3,4,5).

In a similar manner, **23** was converted into 6-(2,3 : 4,5-di-*O*-isopropylidene-1-*O*-mesyl-D-*altro*-pentitol-1-yl)-2-bromopyridine (**27**) in 89% yield, mp 138—139 °C (from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s, iso-Pr), 1.16 (3H, s, iso-Pr), 1.40 (3H, s, iso-Pr), 1.49 (3H, s, iso-Pr), 3.11 (3H, s, Ms), 3.86—4.18 (4H, m, H-3′,4′,5′,5″), 4.99 (1H, dd, H-2′, $J_{1',2'}$ = 7.7, $J_{2',3'}$ = 4.5 Hz), 5.89 (1H, d, H-1′, $J_{1',2'}$ = 7.7 Hz), 7.45—7.68 (3H, m, H-3,4,5). *Anal.* Calcd for $C_{17}H_{24}BrNO_7S$: C, 43.78; H, 5.19; N, 3.00. Found: C, 43.70; H, 5.31; N, 2.93.

6-(α-D-Ribofuranosyl)-2-bromopyridine (6)——Treatment of **27** (350 mg) with CF_3CO_2H/$CHCl_3$ (4 : 1, v/v) (5 ml) as described for the conversion of **4** to **6** afforded a product (172 mg, 79%) which was identical with **6** prepared earlier.

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